VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2016, vol. 87, no. 10, 711–716

ISSN 0017–0011

DOI: 10.5603/GP.2016.0073

Analysis of the origin of birth defects in pregnant women from the Kujawy-Pomerania Region

Anna Lauda-Świeciak, Szymon Bednarek, Jacek Skórczewski, Dariusz Borowski, Mariusz Dubiel

Multi-Specialty County Hospital in Bydgoszcz
Division of Maternal-Fetal Medicine, Gynecology and Neonatology
at Nicolaus Copernicus University Ludwik Rydygier Collegium Medicum in Bydgoszcz

ABSTRACT

Objectives: The aim of the study was to analyze the origin of birth defects in pregnant women from the Kujawy-Pomerania Region, and to identify factors affecting the formation of developmental disorders in the Province.

Material and methods: The correlation between maternal age and fetal defects was investigated. We also attempted to determine whether environmental or family factors play a role in the formation of fetal abnormalities.

Results: The analysis confirmed a correlation between the incidence of chromosomal aberrations and maternal age.

Conclusions: Higher rates of neural tube defects were observed in fetuses born to mothers who did not take folic acid. The influence of other factors on developmental anomalies was not confirmed.

Key words: developmental anomalies, congenital malformations, fetal abnormalities, genetically-determined abnormalities

Ginekologia Polska 2016; 87, 10: 711–716

INTRODUCTION

The beginnings of prenatal diagnostic testing have been dated to the fifth century B.C., when Empedocles described the fetal membranes surrounding a newborn lamb. In the seventeenth century, Francois Mauriceau defined the environment where a fetus is developing as a 'mixture of maternal blood and milk' and coined the term 'amniotic fluid' [1]. However, it was not until the twentieth century, during which Ian Donald introduced the diagnostic ultrasound and Jerome Lejeune linked trisomy 21 with Down's syndrome, that the foundations for the instantaneous development of prenatal diagnostic tests were laid. The first prenatal test in Poland was performed in 1975. In 1992, Kypros Nicolaides started his research on ultrasound markers of chromosome abnormalities, and in 1996 he established the Fetal Medicine Foundation and formed a net of cooperating prenatal diagnosis centers. The discovery of free fetal DNA in circulating maternal blood constituted a breakthrough in contemporary prenatal diagnostics. In 2005, studies on new-generation sequencing were launched and already in 2008 the first non-invasive prenatal test, based on the analysis of fetal DNA, was introduced [2, 3].

OBJECTIVES

The aims of the study were the following:

- determine the cause and incidence of fetal abnormalities diagnosed during the prenatal period in pregnant women from the Kujawy-Pomerania Region;
- establish the genetic background of fetal developmental anomalies;
- identify the nature and distribution of the aberrations;
- select specific predisposing factors for congenital abnormalities in the Province.

MATERIAL AND METHODS

A total of 1021 pregnant women, referred to the Genetic Clinic of Multi-Specialty County Hospital in Bydgoszcz between November 2008 and May 2010 to undergo prenatal diagnostic tests, were recruited. All patients were admitted on the basis of a referral from their ob-gyn in accordance with the NHF guidelines for the Prenatal Screening Program (PSP). Indications for prenatal testing included: advanced maternal age (≥ 35), carriers of chromosome translocations, family or obstetric history of chromosome abnor-

Corresponding author:
Anna Lauda-Świeciak
Multi-Specialty County Hospital in Bydgoszcz, Genetic Clinic, 85–826 Bydgoszcz, ul. Szpitalna 19
tel.: 52 370 93 29, 52 370 91 56, fax: 52 37 09 460

malities as well as congenital malformations or genetically determined diseases, and suspicion of fetal abnormalities in the current pregnancy. Additionally, juvenile patients (< 18 years of age) were included with consent of the statutory representative.

A chart of genetic testing was created for all participants and detailed medical history (family tree, congenital malformations, concomitant diseases in the affected women, their partners and family members of both parties) was obtained. Also, the following environmental factors were analyzed: assisted reproduction, occupational hazards, infections, as well as stimulant and medicine use.

All study participants underwent an ultrasound exam in accordance with the Fetal Medicine Foundation guidelines. Next, venous blood was collected for biochemical screening tests. Patients with fetal defects diagnosed on ultrasound and those at higher risk for fetal aneuploidy in biochemical tests underwent amniocentesis after written informed consent was obtained. Ultrasound reevaluation of the pregnancy was performed again between 18 and 22 weeks of gestation to assess fetal development. If any abnormalities were detected, the test was repeated and the patient was referred to a consultation at a local fetal therapy center. After the tests, each patient received a feedback questionnaire about further development and course of the pregnancy, possible complications, and newborn condition after birth. All patients received genetic counselling, including the estimated risk for defect reappearance in the subsequent pregnancies.

RESULTS

A total of 872 first trimester ultrasound tests (112 abnormal results), 860 first trimester biochemical tests (126 abnormal results), 196 triple tests (28 abnormal results), and 867 second trimester ultrasound tests (73 abnormal results) were conducted. Also, 104 invasive procedures were performed, resulting in 28 abnormal results.

In the study group, 91 congenital defects were found, including 25 (27.5%) cases of genetically-determined abnormalities, 58 (63.7%) cases without known genetic background and 8 complex set of defects with undetermined genetic background. Out of the genetically-determined abnormalities, 80% (20 defects) were chromosome aberrations and 20% (5 defects) were monogenic diseases (Tab. 1, 2).

Defects limited to one organ or system constituted the largest group, with abnormalities of the Central Nervous System (CNS) as the most common (16 patients — 27.6%), followed by defects of the skeletal system (12–20.7%), urogenital system (10 — 17.2%), heart (8–13.8%), digestive system (3–5.1%), and other (9–15.5%) (Fig. 1).

The most common isolated abnormalities included meningocele, hydrocephalus, deformation and defects of the limbs, posterior urethral valve, heart defects — mainly VSD, ASD, AVSD, abdominal wall defect, cleft lip and cleft palate, and cavernous hemangiomas.

Complex, multi-organ defects of undetermined genetic background, including encephalon, heart, chest, and limb defects, as well as cleft palate, were found in 8 patients.

The obtained results were statistically analyzed.

The relationship between the incidence of fetal defects and maternal age was investigated but no correlations between mean maternal age in the groups with and without fetal abnormalities were found. Median age for both groups was 32 years (Tab. 3).

Mean maternal age of women with and without chromosome aberrations was compared. A correlation between maternal age and the incidence of chromosome abnormalities was confirmed. Mean age in patients with the aberration was 34 years, i.e. lower than the age threshold for PSP (Tab. 4).

The effect of environmental factors on the incidence of fetal abnormalities was investigated. No statistically significant differences between the incidence rates in patients at risk and at no risk for harmful environmental factors were found. Regardless, slightly higher rates were detected in women with positive environmental history (place of work, accidental exposure to ionizing radiation, chemicals, and plant protection products during pregnancy) (Tab. 5).

The incidence of fetal defects in women who used folic acid supplementation was analyzed and compared to patients who did not supplement their diet with folic acid. Interestingly, the results were similar for both groups (Tab. 6).

Table 1. Defects with known genetic background

Genetically determined defects			
Chromosomal aberrations (20)		Monogenic diseases (5)	
Numerical (19)	Structural (1)	Recessive (2)	Dominant (3)
Trisomy 21 (11) Trisomy 18 (4) Trisomy 13 (1) Triploidy (1) Monosomy X (1) Mosaic karyotype 46,XX/47XXY (1)	Balanced translocation 46,XY,t(1; 9) (q32; p22)	Osseous dysplasia SLO syndrome	Treacher-Collins syndrome Recklinghausen disease Ectrodactyly

Table 2. Clinical data of patients with chromosome aberrations

No.	Aberration	Maternal age	Paternal age	NT [mm]	β-hCG concentration [ng/mL]	MoM β-hCG	Papp-a concentration [mu/L]	MoM Papp-a	Clinical data
1.	47,XY,+18	45	42	–	–	–	–	–	Common atrioventricular canal Agenesis of the ductus venosus
2.	47,XY,+18	39	43	6.7	41.40	1.26	521.9	0.29	
3.	47,XY,+18	39	42	3.6	17.20	0.34	193.6	0.12	Placental cysts Micrognathia Clenched fist
4.	47,XX,+18	21	21	3.4	10.40	0.24	298.50	0.16	
5.	47,XY,+21	43	43	3.2	45.50	1.91	1299.50	0.44	
6.	47,XX,+21	33	29	5.2	133.60	3.59	2269.10	1.07	
7.	47,XY,+21	30	29	2.7	58.80	1.77	1377.70	0.35	
8.	47,XX,+21	42	44	6.0	280.20	6.17	323.40	0.38	
9.	47,XY,+21	30	32	–	–	–	–	–	Ventriculomegaly Fluid in the pericardium
10.	47,XY,+21	41	55	6.3	109.10	3.02	1309.00	0.73	
11.	47,XX,+21	29	33	3.0	87.40	2.97	2417.60	0.52	
12.	47,XX,+21	41	45	5.4	56.40	1.62	532.50	0.20	
13.	47,XX,+21	29	29	3.5	168.30	4.12	1658.00	0.55	
14.	47,XY,+21	33	34	3.7	156.40	2.87	1189.5	0.59	'In vitro' twin pregnancy Bl.I-obum 10hbd Bl.II- 47,XY,+21
15.	47,XY,+21	41	49	–	–	–	–	–	Triple test, risk for Down's synd. 1:170 (statistically 1:100) β-hCG 1,16 MoM, AFP 1,23 MoM, estriol 2,61 MoM
16.	47,XX,+13	26	29	–	–	–	–	–	Hypotrophy, clenched fist holoprosencephaly, hipotelorism, proboscis
17.	45,X	28	29	7.7	327.70	6.77	923.40	0.43	Cystic hygroma
18.	47,XXY[6]/46,XY[27]	39	36	1.6	173.20	5.11	3921.10	2.27	
19.	69,XXX	27	27	2.5	4.6	0.11	116.60	0.06	
20.	46,XY,t(1;9)(q32;p22)	28	30	8.8	57.60	1.25	2226.60	0.98	

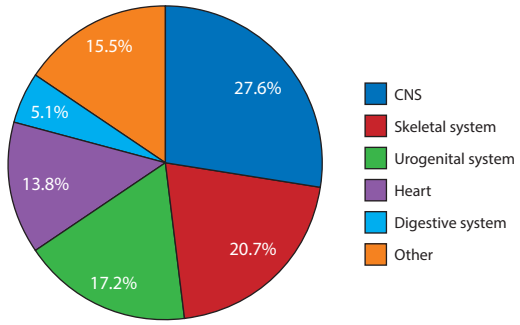

Figure 1. Distribution of the isolated defects

Table 3. Correlation between maternal age and incidence of fetal abnormalities

	Parameters	Subgroups	
		Defect	No defect
	N	91	854
	Min.	18	16
	Max.	45	49
	Median	32	32
	Mean	32.2	32.0
	SD	6.0	5.5
z-test (zcr = 1.96)	z	0.30	
	p	0.76	

Table 4. Correlation between chromosome abnormalities and maternal age

	Parameters	Aberration	
		Yes	No
Age	N	20	71
	Min.	21	18
	Max.	45	45
	Median	33	32
	Mean	34.20	31.63
	SD	6.98	5.58
Shapiro-Wilk Normality test	W	0.922	–
	Wcr	0.905	–
	Normality	yes	–
F Snedecor test (Fcr = 1.93)	F	1.57	
	p	0.18	
t-Student test (tcr = 1.66)	t	1.72	
	p	< 0.05	

Differences in the incidence of CNS defects vs. folic acid intake were studied in the group of 91 women who gave birth to heathy newborns. No statistically significant differences for the level of confidence of 0.05 were observed, although a lower rate was detected in women using folic acid supplementation (Tab. 7).

The literature reports a confirmed positive correlation between folic acid supplementation and decreased rates of CNS defects. In those reports, all pregnant women from the population or patients with unremarkable history constituted the control group. In our study, all patients met at least one of the PSP criteria. In other words, their medical history was not unremarkable and, as such, might have differed from the literature data. Thus, the trend persists but the obtained results are statistical insignificant [4, 5].

DISCUSSION

Genetically-determined diseases have been known for centuries and until today they continue to affect populations all over the world. Delayed motherhood further contributes to the development of chromosome aberrations. At least 20% of all fetuses are affected by chromosome abnormalities but the vast majority spontaneously abort in the early pregnancy. Most fetuses which are miscarried before 9 weeks of gestation present structural defects [6]. A combined interplay of genetic and environmental factors results in the development of fetal abnormalities. All organisms are continuously targeted by numerous mutagenic factors both, endogenous, formed as a result of metabolic processes, and exogenous, resulting from biological, physical, and chemical reactions. Exposure of a developing organism to harmful agents may lead to a teratogenic effect in the form of a congenital defect [7]. It needs to be emphasized that our study population included pre-selected pregnant women, referred to the Genetic Clinic, in accordance with PSP guidelines. All patients met at least one criterion indica-

Table 5. The effect of harmful environmental factors on the incidence of fetal abnormalities

Fetal defects	Harmful factors		No harmful factors		Test for 2 fractions	
	No. of cases	% of cases	No. of cases	% of cases	u	p
Yes	11	14.5%	80	9.2%	1.43	0.15
No	65	85.5%	789	90.8%		
Total	76	100%	869	100%		

Table 6. The effect of pre-pregnancy folic acid intake on the development of fetal abnormalities

Fetal defects	Pre-pregnancy folic acid intake				Test for 2 fractions	
	Yes		No			
	No. of cases	% of cases	No. of cases	% of cases	u	p
Yes	32	9.2%	59	10.9%	0.79	0.43
No	315	90.8%	484	89.1%		
Total	347	100%	543	100%		

Table 7. Correlation between the incidence of CNS and pre-pregnancy folic acid supplementation

CNS defects	Pre-pregnancy folic acid intake				Test for 2 fractions	
	Yes		No			
	No. of cases	% of cases	No. of cases	% of cases	u	p
Yes	3	9.4%	13	22.0%	1.62	0.11
No	29	90.6%	46	78.0%		
Total	32	100%	59	100%		

tive of the need for prenatal diagnosis. The incidence of fetal abnormalities in our study group has been confirmed to be higher as compared to the general population. According to the data from the Polish Registry of Developmental Defects, congenital defects affect 2–4% of all newborns [8]. Similar rates (1.56%) have been reported by E. Kapersky et al. [9]. In the studied population, congenital defects were observed in 9.6% of the women, with 27.5% genetically-determined, 63.7% isolated, and 8.8% complex defects with undetermined genetic background. According to the Polish Registry of Developmental Defects, chromosome aberrations account for 6.5% of congenital defects in live newborns, with 7.5% of monogenic and 50% of multifactorial abnormalities [8]. The incidence of chromosome aberrations in our study was significantly higher (2.1%, i.e. 20 defects in 945 patients) as compared to EUROCAT (30/10000 births) and reports of E. Kapersky et al. (10/10000 births) [9, 10]. Among the isolated defects, the incidence was as follows: CNS (27.6%), skeletal system (20.7%), heart (13.8%), and digestive system (5.1%) defects. According to the Polish Registry of Developmental Defects, the incidence of CNS defects between 2005 and 2006 in the regions included in the Registry was 15.9/10000 births, followed by 70.9/10000 for heart, 42.1/10000 for skeletal system, 9.3/10000 for the digestive system, and 17.2/10000 for complex defects. The incidence of chromosome aberrations was 15.2/10000 births. Data for the entire Province included in the Registry are comparable to numbers in the Kujawy-Pomerania Region [8]. No statistically significant differences were found between mothers from the rural areas and inhabitants of big cities, although the incidence was higher in the former as compared to the latter (12.2% vs. 8.8%, respectively). Kossakowska-Krajewska [11], also failed to observe a statistically significant difference between city and village dwellers, although in her study inhabitants of urban areas had slightly higher occurrence of fetal defects. Antoszewski also analyzed the effect of the environment on the development of cleft lip and cleft palate in the Łódź Region [12]. That study also found no impact of maternal place of inhabitance on the type of the cleft defect. However, Mejnartowicz, quoting Rull R.P., reports a significant effect of parental occupation (agriculture and exposure to plant protection products) on the development of neural tube defects in the offspring [13].

The study group was investigated for a possible correlation between maternal age and defect incidence. No differences were found between mothers of children with birth defects and healthy newborns (mean maternal age was 32.2 and 32 years, respectively). Additionally, age of women who gave birth to children with chromosome aberrations and those with other defects was compared. The result confirmed the role of maternal age in the development of chromosome aberrations although mean maternal age in that group was 34.2 years. Kossakowska-Krajewska [11], reported the highest incidence of congenital abnormalities in women over 35 years of age and confirmed the effect of advanced maternal age on chromosome aberrations. In yet another study [14], the same author emphasized an elevated risk for heart and CNS defects in children born to mothers under 19 and over 35 years of age.

The role of environmental factors on the development of congenital abnormalities has been analyzed. No statisti-

cally significant differences for the level of confidence of 0.05 between endogenous harmful factors and congenital defects were observed. Hozyasz described a link between cleft lip and cleft palate and parental work environment [15], whereas Kossakowska-Krajewska, citing Tesarz, reported no correlation between maternal work in the industrial sector and the development of the abovementioned defects [14].

Most authors who investigated congenital defects focused on their incidence and distribution, or analyzed the causes for their occurrence in one organ or system. Also, studies on the role of one teratogen in the origin of developmental disturbances were conducted or patients with a single factor, e.g. diabetes or thyroid disorders, were investigated. Out study aimed to identify factors promoting developmental disturbances, regardless of the targeted organ or the type of factor. Pregnant women from our study population often had several promoting factors, e.g. age, harmful work environment, or infection in the early pregnancy. Due to the number of potentially teratogenic factors and a wide range of conditions, we did not manage to establish one unambiguous cause for the development of fetal defects in the Kujawy-Pomeranian region.

CONCLUSIONS

Based on the abovementioned results, it seems safe to conclude the following:

— the incidence rates of fetal defects in women referred to the Genetic Clinic of Multi-Specialty County Hospital in Bydgoszcz were higher as compared to mean rates for the Province. Isolated defects are dominant and the CNS abnormalities are the most common;
— in our study, the investigated risk factors had little effect on the development of fetal defects;
— maternal age has a significant influence on the development of chromosome aberrations but no correlation between age and other fetal abnormalities has been detected;
— in light of the fact that a correlation, at the established level of significance, between chromosome aberrations and maternal age (median 33 years) was found, it seems prudent to liberate current criteria for prenatal diagnostic testing as far as maternal age is concerned.

REFERENCES

1. Dangel J. Diagnostyka prenatalna — mity i rzeczywistość. *Nauka.* 2007, 3, 31–47.
2. Donald J. The investigation of abdominal mass by pulsed ultrasound. *Lancet.* 1958, 188–195.
3. Dudarewicz L. Nowe nieinwazyjne testy prenatalne. *Diagnostyka Laboratoryjna, Laboratorium.* 2013, 9–10, 46–47.
4. Brzeziński ZJ. Zapobieganie wrodzonym wadom cewy nerwowej. IMiDZ, Warszawa 1998.
5. Perenc M. Wady ośrodkowego układu nerwowego — etiologia, diagnostyka prenatalna i profilaktyka. *Przew Lek.* 2002, 5, 4, 51–54.
6. Brzeziński ZJ. Choroby uwarunkowane genetycznie — spojrzenie epidemiologa. Medical Scence Review, *Genetyka.* 2004, 128–135.
7. Sąsiadek MM, Stembalska A, Ślęzak R. Problemy teratogenezy w genetyce klinicznej. Med *Sci Rev Genetyka.* 2004, 106–111.
8. http://www.rejestrwad.pl/ Polski Rejestr Wrodzonych Wad Rozwojowych.
9. Kapersky E, Wierzba J, Limon J, [et al.]. Epidemiologia wrodzonych wad rozwojowych zarejestrowanych w województwie pomorskim w latach 2003–2005. *Ann Acad Med. Gedan.* 2008, 38, 25–35.
10. http://www.eurocat-network.eu/ Europejskie Stowarzyszenie Rejestrów Wad EUROCAT.
11. Kossakowska-Krajewska A. Analiza czynników mogących mieć wpływ na ryzyko wystąpienia wrodzonych wad rozwojowych u dzieci urodzonych w województwie warmińsko-mazurskim (1999–2000). Pol Ann Med. 2009, 16 (1), 78–93.
12. Antoszewski B. Wielkość środowiska pochodzenia a częstość występowania rozszczepów wargi i (lub) podniebienia u noworodków z terenu województwa łódzkiego. *Nowiny Lek.* 2007, 76, 5, 414–417.
13. Mejnartowicz JP. Czynniki ryzyka występowania wad cewy nerwowej u dzieci związane ze stanem zdrowia matki dziecka. Wrodzone wady rozwojowe w Polsce w latach 2005–2006. Dane z Polskiego Rejestru Wrodzonych Wad Rozwojowych. Wyd. Naukowe UM, Poznań 2010, 60–65.
14. Kossakowska-Krajewska A. Analiza wad rozwojowych serca i układu naczyniowego oraz układu nerwowego u dzieci urodzonych w województwie olsztyńskim w 1998 roku oraz warmińsko-mazurskim w latach 1999-2000. *Rocznik Medyczny.* 2007, XIV, 1, 35–42.
15. Hozyasz KK. Rozszczepy wargi i (lub) podniebienia a środowiskowe czynniki ryzyka. *Pediatr Pol.* 2005, 80, 2, 180–197.